



Armed Forces College of Medicine AFCM



***Inhibitors and
Uncouplers of
Oxidative
phosphorylation***

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INTENDED LEARNING OBJECTIVES (ILO)



- **By the end of this lecture the student will be able to:**
 1. Categorize the inhibitors of the respiratory chain.
 2. Correlate mitochondrial disorders with clinical diseases.

CASE SCENARIO



- You are part of the team that is called to respond to a possible terrorist attack in an art museum.
- As fumes developed, several people started **choking and collapsing**. The museum authorities tell you 120 people are already pronounced **dead** at the scene.



Cyanide Poisoning



Inhibitors and Uncouplers of Oxidative phosphorylation:



A number of compounds can specifically inhibit electron transfer at different points of the different complexes. These inhibitors will block the oxidation process and prevent the building of a proton gradient.

Inhibition will be on I, III & IV



Insecticide
rotenone.

CN⁻
CO
H₂S

CN⁻ or CO



war gas
dimercaprol

Complex I:



Rotenone, an insecticide binds to complex I and prevents the reduction of ubiquinone.

Amytal and other barbiturates: prevent electron transfer from iron sulfur centers to ubiquinone.

Complex II:



Malonate which acts as a competitive inhibitor of succinate.

Complex III:

Antibiotics inhibit electron transfer through complex III by blocking transfer of electrons from Co Q to iron – sulfur proteins.



Complex IV:

Cyanide and carbon monoxide inhibit Complex IV resulting in impairment of the energy generating function of oxidative phosphorylation. Tissue asphyxia especially of central nervous system occurs leading to death.

Quiz



Cyanide toxicity results from inhibition of:

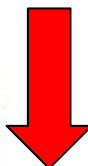
- a. Succinic dehydrogenase
- b. Cytochrome C oxidase
- c. Cytochrome C reductase
- d. PDH
- e. Malate dehydrogenase

Uncouplers of Oxidative phosphorylation



Uncouplers



- short – circuiting the flow of protons through the ATP synthase
- dissociate oxidation in the respiratory chain from phosphorylation
- oxidation rates  , phosphorylation rate 
- result in the production of extra heat

Uncoupling agents



Diverse group of compounds that are

- *Lipid soluble*
- *Act as proton carriers*

*e.g. **2,4 dinitrophenol,**
dinitrocresol*

uncouplers



- (1) 2,4 dinitrophenol (DNP).
- (2) High levels of bilirubin as in cases of hyperbilirubinemia.
- (3) High level of thyroxine as in thyrotoxicosis.
- (4) Snake venoms “their phospholipases”.

(5) Thermogenine



Is a Physiological Uncoupler: it is present in the inner mitochondrial membrane and provides a path for protons to return to the matrix without passing through the F₀ F₁ complex.

- In specific type of adipose tissues called “brown fat” In hibernating animals and in most mammals including human newborns



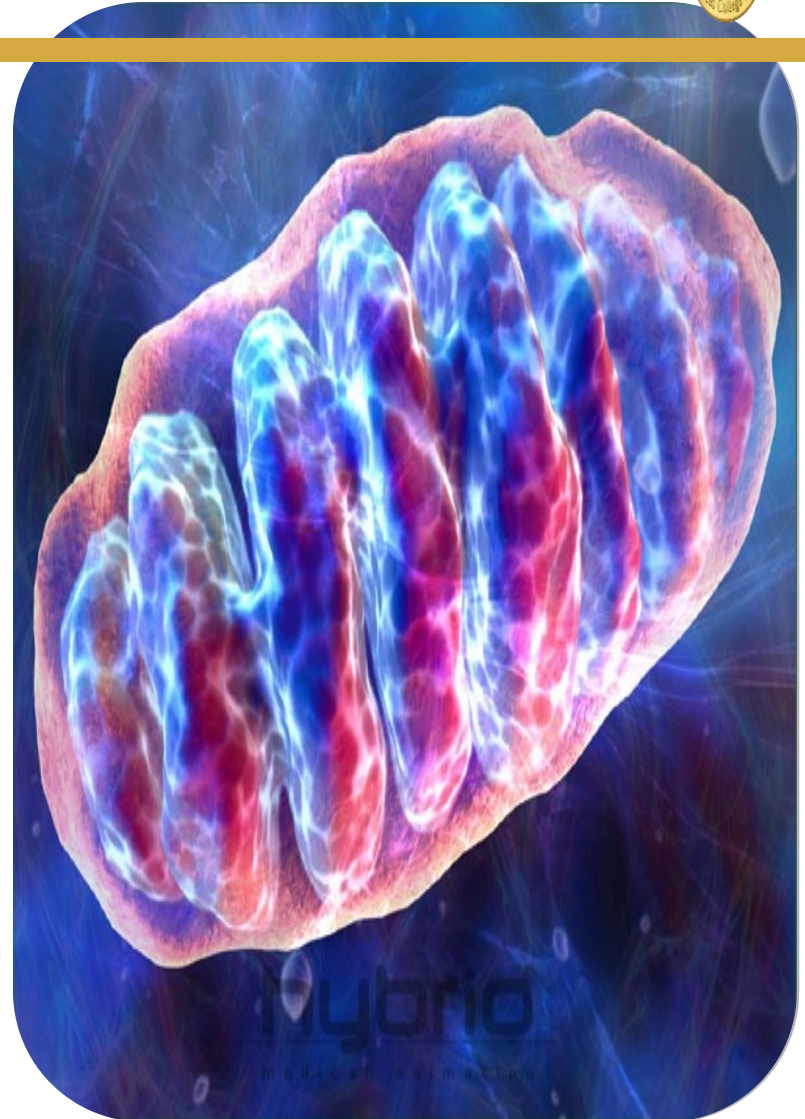
Brown Fat

- **Brown fat** is characterized by high contents of mitochondria and rich blood supply “which give a characteristic brownish colour”. In human infants, it is found at the back of neck. Mitochondria of brown adipose tissues utilize oxidation of fuel not to produce ATP but to generate heat to keep the newborn warm.

What is mitochondria?



- * Power house of the cell**
- * Generate most of the cell's supply of (ATP)**
- * Found in all eukaryotic cells except **RBCs****



Student activity

• **Which of the followings is physiological uncouplers?**

A. 2,4 dinitrophenol (DNP).

B. High levels of bilirubin

C. High level of thyroxine

D. Snake venoms

☒ E. Thermogenin

mitochondria



- The mitochondria contain a circular double – stranded DNA that contain 37
- genes including 13 that encode proteins of the respiratory chain. The remaining genes encode for ribosomal and transfer RNA essential for the protein synthesizing machinery of mitochondria. Other mitochondrial proteins are encoded in nuclear genes.

Mitochondrial diseases

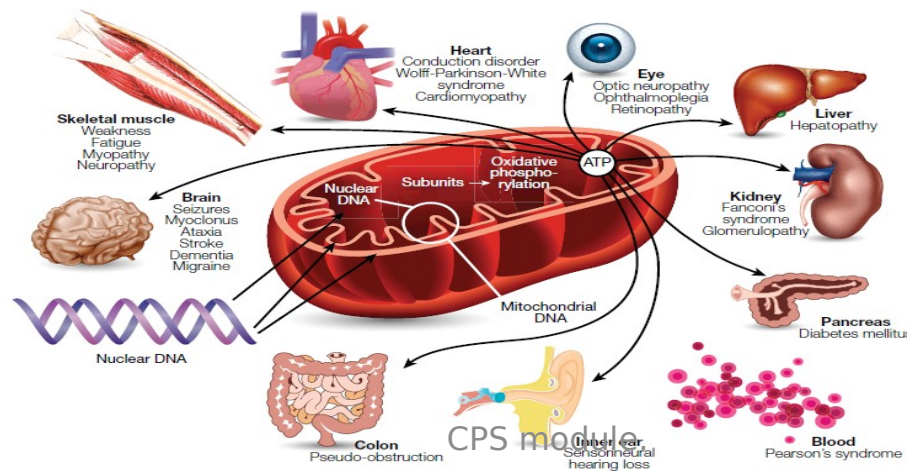


Are heterogeneous multisystem disorders caused by dysfunctional mitochondria where *mitochondria fail to produce enough energy (ATP) for cell or organ function*

Any
age



Both
sex



Any
Organ

Mutations in mitochondrial DNA can lead to a group of human diseases



- Inborn errors of mitochondrial DNA is inherited only from mothers.

They are a group of diseases due to deficiencies in mitochondrial transport function as carnitine system and/or in components of the mitochondrial electron transport chain

Some famous mitochondrial syndromes caused by inherited mtDNA mutations



Key features	Syndrome
Myopathy, encephalopathy, lactic acidosis and stroke-like symptoms	MELAS
and Retinitis pigmentosa Neuropathy, Ataxia, Ptosis	NARP
Myoclonic epilepsy with red ragged fibers on muscle biopsy, hearing loss and lactic acidosis	MERFF

Some famous mitochondrial syndromes caused by inherited mtDNA mutations



Key features	Syndrome
deafness Diabetes mellitus and	MIDD
A rapid decline in function marked by seizures, altered state of consciousness, dementia and ventilatory failure	\$ Leigh

Due to clinical variability existing with mtDNA mutations

Many patients do not fit into one of the famous syndromes

Mutations in mitochondrial DNA can lead to Mitochondrial myopathies



- They are a group of diseases due to deficiencies in **mitochondrial electron transport chain** as NADH dehydrogenase, Cytochrome b or the mitochondrial F₀F₁ ATP synthase. It usually occurs in mitochondria

Diagnosing patients with mitochondrial disease is challenging due to

***The varied clinical presentation (takes many different forms)**



Symptoms of mitochondrial disease (are non specific)

First of all Mitochondrial disease is generally suspected based on one of the following

Presence of a combination of symptoms and signs involving 3 or more different body organs that are difficult to explain
common))

C/p of a patient may Suggest a well recognized mitochondrial syndrome
NOT always seen

Family history of a patient may reveal maternal inheritance pattern

After suspicion of mitochondrial disease, to reach a diagnosis requires the integration of informations obtained from several laboratory tests which includes



1-Metabolic testing (Initial)

- Although they are not specific for mitochondrial disease***
- But their abnormalities may be helpful in supporting an underlying disorder in OXPHOS***

Table 4 Metabolic Testing Abnormalities Supportive of OXPHOS Disease

Blood lactate and pyruvate
Increased blood lactate and pyruvate
Blood amino acids
Increased blood alanine
Urine organic acids
Increase lactate, pyruvate, and Krebs cycle intermediates
Urine amino acids
Generalized aminoaciduria

2-Tissue biopsy from affected tissue (muscle- liver-heart)



**Electron
microscopy**

**Biochemical analysis of RC
complexes**

**Immunohistochemical staining
of tissue**

**Tissue biopsy results highly support the diagnosis
and point to a group of genes may be responsible
for the disease through identifying the faulty
proteins in the chain**

Student activity

- Which of the followings is NOT a character of mitochondrial diseases?
 - A. presented at any age
 - B. Affect multiple organs
 - ☒ C. Affect only females
 - D. Inherited from mothers only

Lecture Quiz



Cyanide toxicity results from inhibition of:

- a. Succinic dehydrogenase
- b. Cytochrome C oxidase
- c. Cytochrome C reductase
- d. PDH
- e. Malate dehydrogenase

SUGGESTED TEXTBOOKS



"Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R. Ferrier.

"Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W. Rodwell.

